DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/11/2011 has been entered.

Receipt is acknowledged of applicant's Amendment/Remarks filed 1/112011. Claim 11 has been amended. Claims 1-10, 12, and 13 are cancelled. Claims 11 and 14-21 are pending and are currently under consideration.

Information Disclosure Statement

2. The information disclosure statement (IDS) filed on 1/26/2011 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement has been considered. However, the NPL reference has not been considered because an English language translation of the document was not provided, and its relevance to the application has not been indicated.

REJECTIONS

3. The following rejections and/or objections are either maintained from the previous Office Action dated 7/12/2010 or newly applied. They constitute the complete set of rejections and/or objections presently being applied in the instant application. It is noted that he maintained rejections have been slightly modified to account for Applicant's amendment of claim 11:

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 11, 14, and 17-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Motitschke et al. (US 6,060,071 – previously cited) in view of Hanifin et al. ("Effects of a Low-potency Corticosteroid Lotion Plus a Moisturizing Regimen in the Treatment of Atopic Dermatitis," *Current Therapeutic Research*, Vol. 59, No. 4, April 1998, pgs 227-233 – previously cited).

The instant claims are directed to a method of treatment of neurodermatitis comprising topical application on affected skin of a dermatological preparation comprising an osmolyte or a pharmacologically compatible salt thereof to a patient in need of such treatment, wherein the osmolyte is ectoine or hydroxyectoine or a pharmacologically compatible salt thereof, wherein said osmolyte results in accelerated healing of the affected skin.

It is noted that on page 2 of the instant specification, neurodermatitis is also termed endogenous eczema or atopic dermatitis.

Motitschke et al. teach cosmetic preparations comprising (S)-1,4,5,6-tetrahydro-2-methyl-4-pyrimidinecarboxylic acid (ectoin) and/or (S,S) -1,4,5,6-tetrahydro-5hydroxy-2-methyl-4-pyrimidinecarboxylic acid (hydroxyectoin) for the care of dry and/or irritated skin, in particular for increasing and/or stabilizing the moisture content of skin (see

abstract; column 1, line 39 to column 2, line 41; column 6, lines 13-17). The compounds (i.e. ectoin and/or hydroxyectoin) are formulated with auxiliaries and/or carrier substances to give a suitable formulation, wherein examples of use forms include ointments, creams, lotions, sprays, etc. as claimed in instant claim 14 (see column 5, lines 1-13). Motitschke et al. also teach other active substances may be added to the product as claimed in the instant claim 17 (see column 5, lines 13-16). Motitschke et al. further teach that in patients suffering from atopy, the symptoms of dry skin or observed irrespective of age, and that the skin condition can be prevented or counteracted by using suitable moisturizing preparation (see column 1, lines 15-30).

Motitschke et al. do not explicitly teach treating neurodermatitis (atopic dermatitis) using the ectoin and/hydroxyectoin compositions.

Hanifin et al. teach that treatment of atopic dermatitis is directed towards reducing inflammation and using moisturizers to maintain a flexible, hydrated stratum corneum (see page 228). Hanifin et al. further teach that the addition of a moisturizer to a low-potency topical corticosteroid lotion (i.e. desonide lotion 0.05%, an antiphlogistic and glucocorticoid as claimed in the instant claims 18) in separate regimens was effective in treating the signs and symptoms of mild-to-moderate atopic dermatitis (see abstract). The addition of the moisturizing cream produced significant reduction of up to 23% in the clinical signs and symptoms of atopic dermatitis, which support and overwhelming patient preference for the desonide/moisturizer combination over desonide alone (see pages 231-232, bridging paragraph; page 232 last paragraph).

It would have been obvious to one of ordinary skill in the art at the time of the invention to treat atopic dermatitis (neurodermatitis) using as moisturizer as taught by Hanifin et al., wherein the moisturizer is the ectoin/hydroxyectoin formulation as taught by Motitschke et al. One of ordinary skill in the art would have been motivated to use the ectoin/hydroxyectoin formulation to treat atopic dermatitis because ectoin/hydroxyectoin formulations improve and stabilize the hydration of the skin. One of ordinary skill in the art would have had a reasonable expectation of success in using the ectoin/hydroxyectoin formulations to treat atopic dermatitis (neurodermatitis) because Motitschke et al. teach that dry skin conditions can be counteracted with said moisturizing preparations, and mention that patients suffering from atopy have dry skin conditions irrespective of age. Further, Hanifin et al. explicitly teach the use of a moisturizer in the treatment of atopic dermatitis.

While the prior art references do not teach the ectoin/hydroxyectoin formulations result in accelerated healing of the affected skin, the application of the formulations to the affected skin is obvious. Since the same patient population is being treated using the same formulation as instantly claimed, the accelerated healing of the affected skin must obviously occur in application of said ectoin/hydroxyectoin formulation.

Thus, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

6. Claims 15-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Motitschke et al. (US 6,060,071 – previously cited) in view of Hanifin et al. (“Effects of a

Low-potency Corticosteroid Lotion Plus a Moisturizing Regimen in the Treatment of Atopic Dermatitis," *Current Therapeutic Research*, Vol. 59, No. 4, April 1998, pgs 227-233). as applied to claims 11, 14, and 17-18 above, and further in view of Touitou et al. ("Liposomes as Carriers for Topical and Transdermal Delivery," *Pharmaceutical Sciences*, Vol. 83, No. 9, Sept. 1994, pgs 1189-1203 – previously cited).

Motitschke et al. and Hanifin et al. are described *supra* as applied to claims 11, 14, and 17-18.

Motitschke et al. and Hanifin et al. do not teach the dermatological preparation comprises liposomes containing the osmolyte (i.e. ectoin, hydroxyectoin, or pharmaceutically acceptable salts thereof).

Touitou et al. teach the advantages of using liposomes as drug carriers for topical delivery, wherein the use of liposomes allows for increased accumulation of the drug in the skin (see abstract; pages 1189-1192, column 1).

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the liposomes taught by Touitou et al. as carriers for the ectoin and/or hydroxyectoin in the method of treating atopic dermatitis obvious over Motitschke et al. in view Hanifin et al. One of ordinary skill in the art would have been motivated to employ liposomes as carriers for the ectoin and/or hydroxyectoin in order to provide the advantages of topical delivery of drugs associated with liposomes, such as the accumulation of the drug in the skin. One of ordinary skill in the art would have had a reasonable expectation of success in employing the liposomes as carriers for ectoin and/or hydroxyectoin because the method of treating atopic dermatitis obvious over

Motitschke et al. in view Hanifin et al. employs a topical composition comprising ectoin and/or hydroxyectoin and Touitou et al. teach the liposomes are drug carriers for topical compositions.

Thus, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

7. Claims 11, 14, 20, and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Motitschke et al. (US 6,060,071 – previously cited) in view of Lodén et al. ("Improvement in skin barrier function in patients with atopic dermatitis after treatment with a moisturizing cream (Canoderm®)," *British Journal of Dermatology*, 1999; 140: pgs 264-267 – previously cited).

The instant claims 20 is directed to method of treatment of neurodermatitis comprising topical application of a dermatological preparation consisting essentially of an osmolyte or a pharmacologically compatible salt thereof to a patient in need of such treatment, wherein the osmolyte is ectoine or hydroxyectoine or a pharmacologically compatible salt thereof. The instant claim 21 is directed to a method of treatment of neurodermatitis comprising topical application of a dermatological preparation comprising ectoine or hydroxyectoine or a pharmacologically compatible salt thereof in the absence of a glucocorticoid.

Motitschke et al. teach cosmetic preparations comprising (S)-1,4,5,6-tetrahydro-2-methyl-4-pyrimidinecarboxylic acid (ectoin) and/or (S,S) -1,4,5,6-tetrahydro-5hydroxy-2-methyl-4-pyrimidinecarboxylic acid (hydroxyectoin) for the care of dry and/or irritated

skin, in particular for increasing and/or stabilizing the moisture content of skin (see abstract; column 1, line 39 to column 2, line 41; column 6, lines 13-17). The compounds (i.e. ectoin and/or hydroxyectoin) are formulated with auxiliaries and/or carrier substances to give a suitable formulation, wherein examples of use forms include ointments, creams, lotions, sprays, etc. as claimed in instant claim 14 (see column 5, lines 1-13). Motitschke et al. also teach other active substances may be added to the product as claimed in the instant claim 17 (see column 5, lines 13-16). Motitschke et al. further teach that in patients suffering from atopy, the symptoms of dry skin or observed irrespective of age, and that the skin condition can be prevented or counteracted by using suitable moisturizing preparation (see column 1, lines 15-30).

Motitschke et al. do not exemplify treating neurodermatitis (atopic dermatitis) using the ectoin and/hydroxyectoin compositions.

Lodén et al. teach patients with atopic skin show a defective barrier function in both rough and in clinically normal skin, and that application of a urea-containing moisturizer to the skin of patients with atopic dermatitis improved skin capacitance indicating skin hydration, improved the water barrier function, and reduced skin susceptibility to irritation by sodium lauryl sulphate (see abstract). Lodén et al. further teach that certain moisturizers could improve the skin barrier function in both normal and atopic skin (see page 267).

It would have been obvious to one of ordinary skill in the art at the time of the invention to treat atopic dermatitis (neurodermatitis) using a moisturizer as taught by Lodén et al., wherein the moisturizer is the ectoin/hydroxyectoin formulation as taught

by Motitschke et al. One of ordinary skill in the art would have been motivated to use the ectoin/hydroxyectoin formulation to treat atopic dermatitis because ectoin/hydroxyectoin formulations improve and stabilize the hydration of the skin. One of ordinary skill in the art would have had a reasonable expectation of success in using the ectoin/hydroxyectoin formulations to treat atopic dermatitis (neurodermatitis) because Motitschke et al. teach that dry skin conditions, including patients suffering from atopy, can be counteracted using suitable moisturizing preparations. Further, Lodén et al. specifically teach the use of a moisturizer cream for improving the skin hydration and barrier function in patients with atopic dermatitis.

While the prior art references do not teach the ectoin/hydroxyectoin formulations result in accelerated healing of the affected skin, the application of the formulations to the affected skin is obvious. Since the same patient population is being treated using the same formulation as instantly claimed, the accelerated healing of the affected skin must obviously occur in application of said ectoin/hydroxyectoin formulation.

In regards to claim 21, it is noted that neither Motitschke et al. nor Lodén et al. teach the preparations contain a glucocorticoid.

Thus, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time it was made.

8. Claims 15-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Motitschke et al. (US 6,060,071 – previously cited) in view of Lodén et al. ("Improvement in skin barrier function in patients with atopic dermatitis after treatment

with a moisturizing cream (Canoderm®)," *British Journal of Dermatology*, 1999; 140: pgs 264-267 – previously cited) as applied to claims 11, 14, 20, and 21 above, and further in view of Touitou et al. ("Liposomes as Carriers for Topical and Transdermal Delivery," *Pharmaceutical Sciences*, Vol. 83, No. 9, Sept. 1994, pgs 1189-1203 – previously cited).

Motitschke et al. and Lodén et al. are described *supra* as applied to claims 11, 14, 20, and 21.

Motitschke et al. and Lodén et al. do not teach the dermatological preparation comprises liposomes containing the osmolyte (i.e. ectoin, hydroxyectoin, or pharmaceutically acceptable salts thereof).

Touitou et al. teach the advantages of using liposomes as drug carriers for topical delivery, wherein the use of liposomes allows for increased accumulation of the drug in the skin (see abstract; pages 1189-1192, column 1).

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the liposomes taught by Touitou et al. as carriers for the ectoin and/or hydroxyectoin in the method of treating atopic dermatitis obvious over Motitschke et al. in view Lodén et al. One of ordinary skill in the art would have been motivated to employ liposomes as carriers for the ectoin and/or hydroxyectoin in order to provide the advantages of topical delivery of drugs associated with liposomes, such as the accumulation of the drug in the skin. One of ordinary skill in the art would have had a reasonable expectation of success in employing the liposomes as carriers for ectoin and/or hydroxyectoin because the method of treating atopic dermatitis obvious over

Motitschke et al. in view Lodén et al. employs a topical composition comprising ectoin and/or hydroxyectoin and Lodén et al. teach the liposomes are drug carriers for topical compositions.

Thus, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

9. Claims 17-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Motitschke et al. (US 6,060,071 – previously cited) in view of Lodén et al. ("Improvement in skin barrier function in patients with atopic dermatitis after treatment with a moisturizing cream (Canoderm®)," *British Journal of Dermatology*, 1999; 140: pgs 264-267 – previously cited) as applied to claims 20-21 above, and further in view of Nghiem et al. ("Tacrolimus and pimecrolimus: From clever prokaryotes to inhibiting calcineurin and treating atopic dermatitis," *J. Am. Acad. Dermatol.*, February 2002, 6(2): pgs 228-241 – previously cited).

The instant claim 19 is directed to a method of treatment of neurodermatitis comprising topical application of a dermatological preparation comprising ectoine or hydroxyectoine or a pharmacologically compatible salt thereof and a calcineurin inhibitor.

Motitschke et al. and Lodén et al. are described *supra* as applied to claims 111, 14, 20, and 21.

Motitschke et al. and Lodén et al. do not teach compositions containing an active agent that is a calcineurin inhibitor.

Nghiem et al. teach tacrolimus and pimecrolimus, topical inhibitors of phosphatase calcineurin (i.e. calcineurin inhibitors), are useful in the topical treatment of atopic dermatitis (see abstract).

It would have been obvious to one of ordinary skill in the art at the time of the invention to treat to treat atopic dermatitis (neurodermatitis) using a ectoin/hydroxyectoin formulation as obvious over Motitschke et al. in view of Lodén et al. in combination with tacrolimus or pimecrolimus as taught by Nghiem et al. One of ordinary skill in the art would have been motivated to combine the ectoin/hydroxyectoin formulation with tacrolimus or pimecrolimus to formulate an effective composition for the treatment of atopic dermatitis. It is obvious to combine individual compositions taught to have the same utility to form a new composition for the very same purpose *In re Kerkhoven*, 626 F.2d 846, 205, U.S.P.Q. 1069 (C.C.P.A. 1980). One of ordinary skill in the art would have had a reasonable expectation of success in combining the ectoin/hydroxyectoin formulation as obvious over Motitschke et al. in view of Lodén et al. with tacrolimus or pimecrolimus as taught by Nghiem et al. because each composition is individually taught or obvious over the prior art for the treatment of atopic dermatitis.

Thus, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time it was made.

Response to Arguments

10. Applicant's arguments filed 1/11/2011 have been fully considered but they are not persuasive.

Applicant argues that the cited prior art does not disclose or suggest that their inventions are capable of resulting in accelerated healing of the affected skin. In response it is respectfully submitted that the application of the while the prior art references do not explicitly teach the ectoin/hydroxyectoin formulations result in accelerated healing of the affected skin, the application of the formulations to the affected skin is obvious over the cited prior art. Since the same patient population is being treated using the same formulation as instantly claimed, the accelerated healing of the affected skin must obviously occur in application of said ectoin/hydroxyectoin formulation to the skin of patients with atopic dermatitis.

Applicant further argues that Motitschke et al. was relevant only to treating the “dry skin” symptoms even in those suffering from atop and not treating atopy itself. In response it is respectfully submitted that treating the symptoms of the atopy is still considered to meet the limitation of "treatment of neurodermatitis." As stated *supra*, the application of the same formulation to the same patient population would obviously result in the accelerated healing of the affected skin as instantly claimed. Furthermore, in response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). For

example, it is noted that Hanifin et al. explicitly teach treatment of atopic dermatitis is in part directed to using moisturizers to maintain a flexible, hydrated stratum corneum (see page 228).

Applicant argues that Applicant's work is based on the insight that ectoine usefulness as treatment of neurodermatitis is - not due moisturizing properties but do to its anti-inflammatory properties and goes beyond the simple treatment of dry skin by improving the barrier function by attacking the cause of neurodermatitis. In response it is respectfully submitted that the mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. *In re Wiseman*, 201 USPQ 658 (CCPA 1979). Since the application of the ectoin/hydroxyectoin formulations to the skin of patients with atopic dermatitis is obvious over the prior art, the discovery by the Applicant of the anti-inflammatory properties of ectoin has no bearing on the patentability of the invention.

Applicant further argues that Lodén et al.'s work on atopic subjects with urea based moisturizer would not have resulted in accelerated healing of the affected skin nor would it have been obvious from Lodén that other moisturizers (such as ectoine) would similarly accelerate skin healing. Applicant also argues that urea is not well tolerated by many patients suffering from neurodermatitis. In response it is respectfully submitted that Lodén et al. clearly teach the improvement of the skin barrier function in patients with atopic dermatitis after treatment of a urea-containing moisturizing cream (see abstract). Lodén et al. also explicitly teach that certain moisturizers could improve

skin barrier function in normal skin and in atopic skin (see page 267). This teaching clearly suggests the use of moisturizers for atopic skin. Motitschke et al. also teach that conditions of atopy and skin condition can be counteracted by suitable moisturizing preparations, wherein a suitable moisturizing preparation is a formulation containing ectoin/hydroxyectoin. Thus, the use of moisturizers, wherein the moisturizer contains ectoin/hydroxyectoin, in atopic skin is clearly taught by the cited prior art. As stated *supra*, the application of the same formulation to the same patient population would obviously result in the accelerated healing of the affected skin as instantly claimed.

Applicant further argues that against the rejection of claim 21, alleging that a person of ordinary skill in the art would not necessarily be motivated to test only moisturizers for treating atopic dermatitis since Hanifin does not disclose moisturizers alone are effective in the treatment of atopic dermatitis. In response it is respectfully submitted that the rejection of claim 21 is based on Motitschke et al. in view of Lodén et al., wherein both references are directed to treating skin with moisturizers.

Thus, for these reasons, Applicant's arguments are found unpersuasive. Said rejection is maintained.

Conclusion

No claims are allowed.

Correspondence

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jody L. Karol whose telephone number is (571)270-3283. The examiner can normally be reached on 8:30 am - 5:00 pm Mon-Fri EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Jody L. Karol/

Examiner, Art Unit 1627

/Yong S. Chong/
Primary Examiner, Art Unit 1627